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JOHN S. PRATT, ESQ
KILPATRICK STOCKTON, LLP
1100 PEACHTREE STREET
SUITE 2800
ATLANTA, GA 30309

EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,773	ROBERTSON ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2010 and 24 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,11,12,15-18,39-41,43 and 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11,12,15-18,39-41,43 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/24/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/30/10 and 11/24/10 has been entered.

2. Claims 1-8, 11, 12, 15-18, 39-41, 43 and 44 are all the pending claims for this application.

3. Claims 1-8, 11, 12, 15-18, 39-41, 43 and 44 are all the pending claims under examination.

Information Disclosure Statement

4. The IDS of 11/24/10 has been considered and entered. The signed and initialed 1449 form is attached.

Rejections Maintained

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. The provisional rejection of Claims 1-8, 11, and 12 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 8 and 9 of copending Application No. 10/417,633 (“the ‘633” application; US 20030232399) in view of Robertson et al. (WO 99/58978; published November 18, 1999; cited in the PTO form-892 of 9/27/06) is maintained.

On pp. 7-8 of the Response of 8/30/10 Applicants defer responding to the rejection until allowable subject matter in the ‘633 application is established. The rejection is maintained.

6. The rejection of Claims 1-8, 11, 12, 15-18, 39-41, 43 and 44 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 7402403 in view of Robertson et al. (WO 99/58978, published 1999, cited in the IDS of 1/13/09) is maintained.

On pp. 7-8 of the Response of 8/30/10 Applicants defer responding to the rejection until allowable subject matter in the instant application is established. The rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

7. The rejection of Claims 1-8, 11, 12, 15-18, 39-41, 43 and 44 under 35 U.S.C. 112, first paragraph, is maintained because the specification does not reasonably provide enablement for the use of the method for detecting any autoantibody against just any tumor antigen for just any cancer, or detecting any autoantibody against just any tumor antigen for just any early neoplastic or early carcinogenic change in asymptomatic patients, or detecting any autoantibody against just any tumor antigen in measuring the recurrence of the cancer or in assessing the prognosis for a treatment therapy much less using only one tumor marker protein antigen.

For purposes of review, the rejection was set forth in the Office Action of 10/1/08 as follows:

> "Nature of the invention/ Skill in the art
>
> The claims are drawn to a method of detecting autoantibodies in a subject by determining a complex formed between a tumor antigen and an autoantibody present in the body fluid and the use of said method in detecting

cancer. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

Breadth of the Claims

Applicants broadly claim a method of detecting autoantibodies to tumor marker proteins prepared from a bodily fluid from a body cavity or space in which a tumor is or was present or associated with in one or more cancer patients comprising contacting a sample of bodily fluids from said subject with one or more tumor markers selected from and determining the presence or absence of said autoantibodies by complex formation with the tumor marker proteins in said bodily fluids, whereby the presence of said complexes is indicative of autoantibodies to the tumor markers (Claim 1). The claims are further drawn to using the method described above, for detecting cancer (Claim 3), monitoring cancer progression or other neoplastic disease (Claim 4), detecting of early neoplastic or early carcinogenic change in asymptomatic patients (Claim 5), screening for a risk of developing cancer (Claim 6), monitoring the response of a patient to an anti-cancer treatment (Claim 7), and/or detecting a recurrent cancer in a subject already having undergone anti-cancer treatment (Claim 8). Claims 11 and 12 depend from Claims 1 and 3, respectively, and are drawn to the kind of bodily fluid from which the one or more tumor marker proteins are obtained.

Disclosure in the specification/ Working examples

The specification teaches that the instant invention relates to the use of a panel assay for the detection of autoantibodies which uses a panel of tumor marker-related antigens, wherein the panel is tailored to detect a particular cancer, or a cancer at a particular state of development (page 17, lines 13-18). With regards to the markers, the specification teaches that preferred markers include c-erbB2, MUC1, Myc, ras, p53, BRCA1, BRCA2, APC, CA125, PSA, CEA and CA19.9 (p. 17, line 25 to page 18, line 7). The specification further provides the following working examples utilizing MUC1 and MUC16 for the detection of autoantibodies of cancer patients:

Example 4 (working) serum from a patient with pleural effusions and serum from a patient with advanced breast cancer showed auto-reactive antibodies against MUC1 (Figure 4) compared to normal controls (Figure 5). Serum from patients with ovarian masses and ascites from a patient with breast cancer showed auto-reactive antibodies against MUC16 antigen (Figure 6).

Example 7 (working) MUC1 protein purified from pooled ascetic fluid and pleural effusion from patients with advanced breast cancer showed the protein to be as reactive to autoantibodies as the individually isolated MUC 1 protein (Figures 10 and 11).

Thus, while the specification clearly sets forth the presence of autoantibodies in a patient to MUC1 and MUC16 and using purified proteins for MUC1 and MUC16 in a panel assay for detecting cancer, the specification appears to be silent on the presence of autoantibodies to just any tumor antigen found in any bodily fluid from any body cavity or space and whether the presence of autoantibodies to these tumor antigens, alone or in combination, can be used for the detection of any cancer, monitoring any cancer progression or other neoplastic disease, detecting of early neoplastic or early carcinogenic change in asymptomatic patients, screening for a risk of developing any cancer, monitoring the response of a patient to any anti-cancer treatment, and/or detecting any recurrent cancer in a subject already having undergone any anti-cancer treatment. As such, if there is no correlation, then the examples do not constitute working examples. While it is understood that the absence of working examples should never be the sole reason for rejecting claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment of cancer, is required for practice of the claimed invention.

Quantity of experimentation

The quantity of experimentation in the areas of cancer diagnosis utilizing autoantibodies is extremely large given the unpredictability associated with only subsets of patients with a tumor developing a humoral-based autoantibody response to a particular antigen and the lack of knowledge pertaining to the presence of autoantibodies to any caner-associated antigen being indicative of a particular cancer.

State of the prior art/ Unpredictability of the art

The state of the art at the time of filing was such that one of skill could recognize that the use of autoantibodies as serological markers for cancer diagnosis is an interesting concept because of the general absence of these autoantibodies in normal individuals and non-cancer conditions. For example, Stockert et al. (J. Exp. Med. 1998; 187: 1349-1354) teaches that there are a variety of known immunogenic human tumor antigens which generally fall into one of the following categories" (a) cancer-testis antigens; (b) antigens coded for by mutated genes, e.g., p53 and DCK4; (c) differentiation antigens, e.g., tyrosinase and Melan-A; (d) amplified gene products, e.g., Her2/neu and carbonic anhydrases; and viral antigens, e.g., retrovirus, HPV and EBV. In particular, Stockert et al. teach that a survey of sera from 234 cancer patients showed autoantibodies to NY-ESO-1 in 19 patients, to MAGE-1 in 3, to MAGE-3 in 2, and to SSX2 in 1; and no reactivity in sera from 70 normal individuals (page 1351, Table 2).

Likewise, Zhang et al. (Cancer Epidemiology, Biomarkers & Prevention 2003; 12: 136-143) examined the reactivity's of several hundred sera from patients with six different types of cancer to a mini-array of seven selected tumor associated antigens (page 137, 1st column, 1st paragraph). Interestingly, Zhang et al. found that the frequency of antibodies to any individual antigen rarely exceeded 15 to 20%, but with the successive addition of antigens to the panel, there was a stepwise increase in the percentage of positive reactors to between 44 and 68% against a combined panel of seven antigens (page 137, 1st column, 1st paragraph). More recently, Casiano et al. (Molecular & Cellular Proteomics 2006; 5: 1745-1759) lists over 40 candidate tumor associated antigens (TAAs) recognized by autoantibodies from prostate cancer patients. In particular, Casiano et al. teach that while tumor associated antigen (TAA) arrays provide a promising and powerful tool for enhancing cancer detecting and treatment; their utility in a clinical setting is currently in its infancy (page 1755, 2nd column, last paragraph). Thus, while these references cited above clearly show that autoimmunity can be associated with cancer in the form of the development of autoantibodies to autologous cellular antigens, the state of the prior art recognizes the unpredictability associated with cancer diagnosis utilizing autoantibodies because only subsets of patients with a tumor develop a humoral response to a particular antigen

The claims are not limited to any kind of tumor antigen panel or any cancer shown to have a correlation with tumor antigen expression and the detection of autoantibodies to the tumor antigen protein. However, if the ordinary artisan were to consider the art for any class of tumor antigens, using CYFR 21-1, annexin I and annexin II as examples, the state of the prior art at the time the invention was made recognizes that each represent diagnostic markers for a variety of cancerous conditions, as well as non-cancerous conditions. Both Steiber et al. (Cancer 1993; 72: 707-713) and Muraki et al. (Cancer 1996, 77: 1274-1277) found high levels of CYFR-1 in the sera of patients suffering from lung cancer. In addition to being a marker for lung cancer, Muraki et al. also teach that CYFRA 21-1 is useful as a tumor marker for breast carcinoma and gynecological malignant neoplasms, and further, has been reported to be present at high levels in benign respiratory diseases, pulmonary tuberculosis, and intestinal pneumonia (page 1277, 1st column, last 2 full paragraphs). Similarly, both annexin I and annexin II have been shown to be expressed in a variety of tumors. For example, Brichory et al. (PNAS 2001: 98; 9824-9829) teach that both annexin I and annexin II are expressed in lung carcinomas (page 9827, Figure 4). Brichory et al. further teach that increased Annexin II expression is also associated with glioblastoma multiforme, pancreatic cancer and acute premyelocytic leukemia (page 9829, 2nd column, paragraph bridging column 1 and column 2). Thus, while the prior art recognizes that CYFRA 21-1, annexin I and annexin II represent diagnostic markers for a variety of cancerous conditions, as well as non-cancerous conditions, only autoantibodies to annexin I and annexin II, and not autoantibodies to CYFRA 21-1, have been taught in the prior art. For instance, Brichory et al. teaches that sera from 54 newly diagnosed patients with lung cancer, 60 patients with other cancers and 61 noncancer controls were analyzed for the presence of autoantibodies to annexin I and annexin II (page 9825, Table I). Specifically, Brichory teaches that sera from more than half of the patients with lung cancer exhibited autoantibodies to annexin I and/or annexin II, but only autoantibodies to Annexin II were found only in lung cancer patients in our series, whereas annexin I autoantibodies were observed in a few patients with other cancers. Thus, while the studies conducted by Brichory et al. clearly suggest a correlation between some patients with lung cancer and the presence of autoantibodies to annexin I and/or annexin II, the percentage of patients having such autoantibodies is small compared to the total population and does not appear to suggest that the presence would be indicative of cancer (emphasis added).

A similar analogy can be made for the class of MUC1 or MUC16 cancer antigens and autoantibodies in detecting any disorder much less the correlation between the antigen expression, presence of autoantibody and the disease type. As an example, Treon et al. (Blood 96(6):3147-3153 (2000)) teach that there is an inverse relationship between soluble MUC1 expression in serum and the level of detectable IgM and IgG autoantibody in patients with multiple myeloma. The studies of Treon teach both IgM and IgG antibodies to MUC1 were detected in MM patients, however, the mean levels of both IgM- and IgG-circulating antibodies were lower than those detected in health humans (Table 2), soluble MUC1 were significantly higher in MM patients versus health patients, and mean soluble MUC1 levels were inversely related to mean anti-MUC1 antibody levels among MM patients and healthy patients (Table 1) (p. 3151, Col. 1, ¶1). Thus the value in detecting autoantibodies at least against MUC1 tumor antigen in MM patients would not have been correlative with disease presence nor could detecting MUC1 antibodies in any cancer patient as instantly claimed provide a basis for detection of any cancer, monitoring any cancer progression or other neoplastic disease, detecting of early neoplastic or early carcinogenic change in asymptomatic patients, screening for a risk of developing any cancer, monitoring the response of a patient to any anti-cancer treatment, and/or detecting any recurrent cancer in a subject already having undergone any anti-cancer treatment.

As to correlating disease specificity with the detection MUC 16 (CA125), Szekanecz et al. (Ann. NY Acad Sci 1108:359-371 (2007) Abstract) teaches that the tumor antigen, CA125 (MUC16) is increased (10.8%) in patients serum with rheumatoid arthritis measured by immunoassay compared to controls (7.1%). Thus not only is MUC 16 expressed in serum of normal subjects but to a greater extent in a cancer-unrelated disorder. These studies establish that there is no strict correlation between MUC 16 tumor markers in a body cavity from a subject and the correlation

to cancer. Still further, it us even less tenable how the detection of autoantibodies would be a diagnostic indicia for cancer under these circumstance.

In the instant case, if autoantibodies to MUC1 and/or MUC16 are to be considered as a surrogate for a disease state, a specific disease state must be identified in some way with the molecule. There must be some pattern that would allow the autoantibodies to MUC1 and/or MUC16 to be used in a consistent, specific, predictable and verifiable diagnostic manner for a particular disease. For example, as noted above, those of skill in the art recognize that the antigens MUC1 and MUC16 have been individually taught to be variable insofar as their correlative accuracy in diagnosing any kind of cancer. In the absence of any correlation between the instant claimed autoantibodies with any known disease or disorder, any information obtained from various expression profiles in both normal and diseased tissue only serves as the basis for further research on the observation itself. Therefore, absent evidence of the autoantibodies presence including the correlation to a diseased state, one of skill in the art would not be able to predictably use the antigen in any diagnostic setting without undue experimentation. Autoantibody assays against a panel of antigens could be used as an aid to art-recognized, standardarized cancer detection/monitoring procedures but as a stand alone diagnostic, the claimed method is not enabled.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlating success, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

The rejection was maintained in the Office Action of 6/1/09 as follows:

"Applicants allegations on p. 9 of the Response of 3/5/09 have been considered and are not found persuasive. Applicants allege "The examples of the present application describe the preparation of several tumor marker proteins, such as MUC1, MUC16, and c-myc. Sources of antibodies for purification of numerous other tumor marker proteins are provided on page 38 of the present specification."

Response to Arguments

Arguments of counsel alone are not found to be sufficient in overcoming the enablement rejection (MPEP 2144.03).

The examiner cited several art references explaining the difficulty in predicting correlation between the presence of MUC1 and MUC6 autoantibodies and being able to distinguish a cancer from a non-cancer because the references taught that MUC1 and MUC6 autoantibodies were found in cancerous and non-cancerous diseases alike. Further, none of the elected generic claims are even drawn to a tumor antigen that is strictly and uniquely associated with a cancer and for which autoantibodies are detected. None of the method claims are drawn to using some other art-recognized clinical criteria or markers for a particular cancer that would exclude non-cancerous disorders otherwise associated with co-expression of autoantibodies and the same target antigen.

Further, Applicants have not addressed the issue of overcoming tolerance in those instances where the tumor antigen is found to be expressed in both normal tissues and cancerous tissues, for example, CD20. CD20 is ordinarily found on some populations of B cells but overexpressed in B cell malignancies, and therefore in order to generate an autoantibody, one would seemingly have to overcome tolerance to CD20. The same applies to the myriad antigens and autoantibodies encompassed by the instant claims. Applicants have not shown and the prior art does not support overcoming tolerance to any expressed tumor antigens for any cancer to the extent that auto-antibodies are generated much less that they can be used as an indicia for a predictable cancer detection methods.

The ordinary artisan would not have been reasonably apprised of how to practice using the methods absent further detailed and undue experimentation in order to determine a) the correlation for autoantibodies and cancer specific expression of any tumor antigen or b) the presence of autoantibodies against antigens found on both normal and cancerous tissues. The rejection is maintained.

The rejection was maintained in the Office Action of 12/8/09 as follows:

"Applicants' allegations on pp. 10-12 of the Response of 10/1/09 have been considered and are not found persuasive. Applicants allege the method is clarified by amending the claims to recite the tumor marker proteins are over- expressed or altered forms of wild-type proteins; the Figures of the present application show the usefulness of several antigens of the claimed methods (MUC1, MUC16 and c-myc) and show successful detection of various cancers (breast, ovarian and sarcoma) in patients, even in asymptomatic patients prior to cancer diagnosis.

Response to Arguments

Working examples for which the method invention is enabled are muc1/breast cancer; CA125/ovarian cancer; and MUCl/sarcoma where each of the species has a structure function correlation and for which Applicants have demonstrated that tolerance to self-antigen can be overcome. The breadth of the claim scope exceeds what is enabled as taught in the specification and the prior art. Applicants have not shown that the myriad anti-tumor autoantibodies can be generated against just any over-expressed tumor marker protein or any altered forms of just any wild-type protein and that would yield a tumor marker capable of being antigenic.

Also, as discussed above in the Office Action of 10/1/08, references cited and discussed clearly show that while autoimmunity can be associated with cancer in the form of the development of autoantibodies to autologous cellular antigens, the state of the prior art recognizes the unpredictability associated with cancer diagnosis utilizing autoantibodies because only subsets of patients with a tumor develop a humoral response to a particular antigen.

Finally, several technical questions remain unanswered and that go to the issue of whether the ordinary artisan would be enabled to practice the method invention. What is the level of over-expression for a tumor marker that results in the generation of autoantibodies and that otherwise goes undetected by the humoral response? Does every tumor marker protein that's over-expressed on a given tumor or in a given cavity stimulate auto-antibody production? What are the conditions for inducing an autoantibody response? What antigens are uniquely expressed on tumors and that would allow the ordinary artisan to conclude that the patient sample being detected of having an autoantibody was an autoantibody against only a tumor marker antigen? What are the possibilities that some or even rare instances of non-cancerous disorders would also express the same antigen that bears the same properties as the tumor marker antigen that is over-expressed or altered from the wild-type and that if detected in the assay, could lead to an erroneous false positive assessment for cancer of that patients sample?

Furthermore, what properties define the genus of alterations to a wild-type protein that result in it's being a tumor marker? What alterations are required to generate an autoantibody against any one of these proteins that is not otherwise present in the wild type protein? The alterations to the wild type protein require that it a) result in being a tumor marker, and b) result in generating an autoantibody response in a patient subject? What class of proteins meets this requirement?

Applicants' amendments to the claims beg more technical questions than resolve the outstanding issues for the lack of enabling disclosure. The rejection is maintained.

The rejection was maintained in the Office Action of 8/30/10 as follows:

"Applicants allegations on pp. 8-9 of the Response of 3/8/10 have been considered and are not found persuasive. Applicants allege: i) by emphasizing what the claimed invention is or how it is recited rather than by what it is not or does not recite, is seemingly the answer to this outstanding rejection for lack of enablement; and ii) three working examples in a patent application is more than sufficient for a showing of enablement where Applicants have shown a correlation for MUC1/breast cancer, CA125/ovarian cancer, and MUC1/sarcoma.

Response to Arguments

First, Applicants are incorrect in their understanding of the law for enablement under 35 U.S.C. 112, first paragraph. "[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and *use the full scope* of the claimed invention without 'undue experimentation.'" *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993)). It is the examiner's position that it would require undue experimentation to screen the universe of over-expressed tumor-marker proteins much less the altered forms of wild-type proteins in order to identify autoantibodies to the tumor markers.

Second and according to the MPEP 2138.05 in citing *Birmingham v. Randall*, 171 F.2d 957, 80 USPQ 371, 372 (CCPA 1948) "To establish an actual reduction to practice of an invention directed to a method of making a product, it is not enough to show that the method was performed. "[S]uch an invention is not reduced to practice until it is established that the product made by the process is satisfactory, and [ ] this may require successful testing of the product." The method must be useful for detecting a reasonable number of anti-tumor marker autoantibodies against the universe of over-expressed tumor-marker proteins much less any altered forms of wild-type proteins, otherwise what purpose would be served by practicing the method?

Third and finally, the *Wands* court did not establish what a reasonable number of species should be in establishing the scope of enablement for a genus. The *Wands* decision does not provide any guidance as to what a reasonable number of working examples should be. Specifically the Court stated:

"No evidence is presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen."

Applicants allegations on pp. 8-9 of the Office Action of 8/30/10 have been considered and are not found persuasive

Applicants allege the claims are enabled by virtue of the fact of what and how they are claiming the subject matter for performing the method. Applicants assert that it is not understood how Claims 15 and 16 remain rejected when the examiner has stated that the method is enabling for MUC 1/breast cancer, CA 125/ovarian cancer, and MUC1/ sarcoma.

Response to Arguments

Initially, the examiner submits that Applicants have failed to establish which of the myriad cancers over-express tumor marker proteins to the extent that a cancer-associated anti-tumor autoantibody would be formed against an antibody to the tumor marker (see lines 10-12 of Claim 1). Applicants have also failed to establish which of the myriad cancers express tumor marker proteins that are altered wild-type proteins and to the extent that a cancer-associated anti-tumor autoantibody would be formed against an antibody to the altered wild-type protein(s) (see lines 10-12 of Claim 1). MPEP 2163 states in part:

"In such instances the alleged conception fails not merely because the field is unpredictable or because of the general uncertainty surrounding experimental sciences, but because the conception is incomplete due to factual uncertainty that undermines the specificity of the inventor's idea of the invention. Burroughs Wellcome Co. v. Barr Laboratories Inc., 40 F.3d 1223, 1229, 32 USPQ2d 1915, 1920 (Fed. Cir. 1994)").

Secondly, where Claims 15, 16, 17 and 18 recite species of tumor markers with

which the invention is allegedly enabled for practice, the species are not even defined by the cancers on which they are over-expressed or whether the species represent an altered wild-type protein. There is an overwhelming ambiguity to the scope of the cancers and tumor -associated markers that would permit overcoming or breaking tolerance to any given marker with the result of producing an initial antibody much less where as in the present case, the subject is endowed with protective anti-tumor autoantibodies against the initial antibody and against the tumor.

Thirdly, it is not even established that the method could be practiced looking at only one tumor-associated antigen as the claims read. The references in the art teach that multiple antigens would need to be assessed for a cancer determination.

Finally, as discussed in the interview of 8/25/10 and excerpted from the Advisory Action of 9/27/10 “the tumor marker proteins must meet the following structure/function criteria under the instant claims: i) found in bodily fluid/space/cavity around a tumor, ii) over-expressed by the tumor, iii) altered forms of a wild type tumor protein are found/isolated, and iv) the tumor antigen (wild-type or mutant) must be auto-reactive/ antigenic in order to generate auto-antibodies. The nature and kind of tumor antigens encompassed by the claims would require undue experimentation to identify a tumor protein meeting all of the structure/function requirements.”

The rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. The rejection of Claims 1-8, 11, 12, 15-18, 39-41, 43 and 44 under 35 U.S.C. 102(b) as being anticipated by Robertson et al. (WO 99/58978, published 1999, cited in the IDS of 1/13/09) is maintained.

The rejection was set forth in the Office Action of 6/1/09 as follows:

"The interpretation of Claims 1-8, 11, and 12 is of record. New Claims 39-44 are interpreted as being drawn to the method where the tumor marker protein is isolated by protein purification techniques (Claim 39), the fluid samples are pooled from patients for protein purification (Claim 40), the isolated antibody is substantially free from immunoglobulin (Claim 41), the bodily fluid is not from systemic circulation (Claim 42) and is not whole blood or serum (Claim 43) and where the bodily fluid is produced as a result of the disease process or presence of cancer cells (Claim 44).

Robertson teach a method of detecting an autoimmune antibody response to a mammal to circulating tumor marker proteins or tumor cells expressing said tumor marker proteins, which method comprises steps of contacting a sample of bodily fluids obtained from a space associated with a cancer with a panel of two or more distinct tumor marker antigens and determining the presence or absence of complexes of said tumor marker antigens bound to autoantibodies present in said sample of bodily fluids, wherein the presence of said complexes is indicative of an immune response (page 5, lines 2-21). The tumor proteins are taught as being purified from patient fluids such as for example, in Example 1 and 2. The WO reference teaches examples of bodily fluids which may or may not be whole blood or serum from systemic circulation (p. 8, lines 6-12), or specifically obtained from a cavity or space including pleural effusion, ovarian cyst and colon polyps (Fig. 11; p. 45, lines 14-15) and which may be pooled from different patients (Example 1).

With regards to the panel of tumor markers, the WO document teaches that the panel includes, but is not limited to, MIUC1, c-erbB2, c-Myc, p53, ras, BRCA1, BRCA2, APC, PSA and CA125 (page 8, lines 1-20), and tailoring the tumor marker antigens with regard to a particular application (p. 10, line 11- to p. 11, line 25).

Moreover, the WO document teaches that the method is useful in a variety of clinical situations such as in the detection of primary or secondary (metastatic) cancer, in screening for early neoplastic or early carcinogenic change in asymptomatic patients or identification of individuals 'at risk' of developing cancer (particularly breast cancer, bladder cancer, colorectal cancer or prostate cancer) in a population or asymptomatic individuals, in the detection of recurrent disease in a patient previously diagnosed as carrying tumour cells who has undergone treatment to reduce the number of tumour cells or in predicting the response of an individual with cancer to a course of anti-cancer treatment (page 9, lines 17-30 and page 31, lines 21 +). The WO document further teaches a method of determining the immune response of a patient to two or more circulating proteins or to tumor cells expressing said tumor maker proteins and identifying which tumor marker elicits the strongest immune response (page 11, line 27 to page 12, line 19). Finally, the WO reference teaches isolating the protein by protein purification techniques including immunoaffinity separation where the eluted protein fraction is free from immunoglobulin (Example 1 and 2).

The rejection was maintained in the Office Action of 12/8/09 as follows:

"Applicants allegations on pp. 12-13 of the Response of 10/1/09 have been considered and are not found persuasive. Applicants allege page 5, lines 8-10 of Robertson describe contacting a sample of bodily fluids from a mammal with a panel of two or more distinct tumor marker antigens. The sample of bodily fluids is the test sample being analyzed in the assay, not the source of the antigen used in the assay. Similarly, on page 45, lines 14-15, the reference to pleural effusion, ovarian cysts and colon polyps refers to evidence of malignancies that six patients (misdiagnosed using conventional methods as being the "benign" group, but correctly diagnosed using the method

taught by Robertson) were subsequently found to have. These malignancies were eventually diagnosed as lung cancer, skin cancer and adenocarcinoma. (See page 45 of Robertson, lines 7-20.)

Response to Arguments

The examiner respectfully disagrees with Applicants' assertion that Robertson does not teach that the tumor antigens are not taken from bodily fluids.

Robertson teaches in the context of the assay for detecting tumor marker autoantibodies that:

"The panel assay of the invention uses a panel of tumour marker-related antigens. The panel may be tailored to detect a particular cancer, or a cancer at a particular stage of development. The tumour marker antigens may be wild type or mutant tumour marker proteins isolated from samples of biological fluid from normal individuals or from cancer patients or from cell lines expressing the tumour marker protein or they may be full length recombinant tumour marker proteins, viral oncogenic forms of tumour marker proteins or antigenic fragments of any of the aforementioned proteins. The term "antigenic fragment' as used herein means a fragment which is capable of eliciting an immune response (p. 7, lines 9-22)"

"As aforementioned, the assays can be formed using tumour marker antigens which are forms of these proteins isolated from human bodily fluids or from cultured cells or antigenic fragments thereof or full length or truncated recombinant proteins or antigenic fragments thereof (p. 8, lines 21-27).

"As used herein the term 'bodily fluids' includes plasma, serum, whole blood, urine, sweat, lymph, faeces, cerebrospinal fluid or nipple aspirate. The type of bodily fluid used may vary depending upon the type of cancer involved and the use that the assay is being put to. In general, it is preferred to perform the method on samples of serum or plasma (p. 6, lines 6-13)."

The examiner submits that the bodily fluids in Robertson that are not from the systemic circulation but which are otherwise found in a cavity or space where a tumor is or was present includes: urine (bladder), lymph (wound drainage or hydrocoele), faeces (colorectal or intestinal), or cerebrospinal fluid (meninges). Thus Robertson teaches a method using tumor markers obtained from potential fluids obtained from cavities or spaces that read on the generic and dependent claims. The rejection is maintained.

The rejection was maintained in the Office Action of 8/30/10 as follows:

"Applicants' allegations on pp. 9-11 of the Response of 3/8/10 have been considered and are not found persuasive. Applicants allege "Robertson fails to teach the preparation of tumor marker proteins from a bodily fluid from a body cavity or space in which a tumor is or was present in one or more cancer patients as claimed in the present application."

Response to Arguments

The examiner's interpretation the phrase in Claim 1 "wherein the immunoassay reagent comprises one or more tumor marker proteins *prepared* from a bodily fluid from a body cavity or space in which a tumor is or was present in one or more cancer patients and the bodily fluid is not a fluid derived from the systemic circulation" is given the broadest reasonable interpretation consistent with the specification. See *In re Morris*, 127 F.3d 1048, 44 USPQ2d 1023 (Fed. Cir. 1997) and MPEP 904.01.

Specifically, the term "prepared" is interpreted as meaning isolated or extracted and which as discussed above is taught by Robertson.

Specifically, the phrase "a bodily fluid from a body cavity or space" is interpreted as meaning: urine (bladder), lymph (wound drainage or hydrocoele), faeces (colorectal or intestinal), or cerebrospinal fluid (meninges) and all of which comprise a fluid from a space or cavity and which as discussed above is taught by Robertson."

Applicants allegations on pp. 9-11 of the Response of 8/30/10 have been considered and not found persuasive. Applicants allege the term "bodily fluid" of the Robertson publication clearly describes only the bodily fluid sample being tested by the

assay, not the biological fluid source from which the tumor marker antigens are prepared.

Response to Arguments

The examiner's comments from the Advisory Action of 9/27/10 are excerpted as follows:

"In the interview of 8/25/10, Applicants explained the difference between patient sample (bodily fluids) in Robertson as being the source from which the auto-antibodies are detected from the patient and are measured versus the source of the tumor proteins being from the proximity to the tumor in a cavity or space. Applicants emphasized that the second step of the method;- isolating the tumor antigens, is the critical inventive step and that the Robertson reference did not contemplate this step.

Irrespective of whether the Robertson reference did or did not specifically contemplate the second step of the claimed method, Robertson meets the requirements of a 102 reference for teaching the method steps. The examiner has re-searched the Robertson WO reference using the search terms "biological fluid" (1 hit) and "bodily fluid" (36 hits). After careful inspection of the hits for "bodily fluid", Robertson does not distinguish a "bodily fluid" being the source for the tumor antigenic protein and the test sample for the auto-antibody against the tumor antigen. "Bodily fluids" are defined on p. 6, lines 6-9. The source of the tumor marker proteins are described as being from "bodily fluids" on p. 8, lines 21-27. The auto-antibodies from patient samples are defined as being from "bodily fluids" (p. 6, lines 1-6). Thus, the conclusion to be drawn is that the test sample from the patient and the biological fluid containing the tumor markers can be one in the same as defined by a "bodily fluid" under Robertson."

The rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

9. The rejection of Claims 1-8, 11, 12, 15-18, 39-41, 43 and 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained because the specification and the prior art do not support the breadth of scope for the genus of autoantibodies because the scope of tumor antigens is undefined and unlimited.

The rejection was set forth in the Office Action of 12/8/09 as follows:

"Under the Written Description Guidelines (66 FR 1099 (Jan. 5, 2001); 1242 O.G. 168 (Jan. 30, 2001) revised training materials Mar 25, 2008), the claimed invention must meet the following criteria as set forth.

a) Actual reduction to practice: the specification provides the following working examples utilizing MUC1 and MUC16 for the detection of autoantibodies of cancer patients:

Example 4 (working) serum from a patient with pleural effusions and serum from a patient with advanced breast cancer showed auto-reactive antibodies against MUC1 (Figure 4) compared to normal controls (Figure 5). Serum from patients with ovarian masses and ascites from a patient with breast cancer showed auto-reactive antibodies against MUC16 antigen (Figure 6).

Example 7 (working) MUC1 protein purified from pooled ascetic fluid and pleural effusion from patients with advanced breast cancer showed the protein to be as reactive to autoantibodies as the individually isolated MUC 1 protein (Figures 10 and 11).

b) Disclosure of drawings or structural chemical formulas: the specification and drawings do not show that applicant was in possession of the genus of anti-tumor autoantibodies or their intended target antigen expressed by any tumor in any cavity or space from any patient.

c) Sufficient relevant identifying characteristics: the specification does not identify 1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with correlation between structure and function for the genus of tumor marker antigens and the autoantibodies recognizing those antigens.

d) Method of making the claimed invention: the specification teaches screening for autoantibodies and isolating tumor antigens in general but does not identify the genus of tumor marker protein where the protein is either over-expressed or an altered form of a wild-type protein from a bodily fluid from a body cavity or space in which a tumor is or was present in one or more cancer patients. In the absence of a reasonable number of tumor marker protein examples meeting the claim limitations, the ordinary artisan would conclude that applicants were not in possession of the genus of autoantibodies against those proteins.

e) Level of skill and knowledge in the art: the art of screening for autoantibodies against one or more purified tumor marker proteins in an immunoassay format wwouod have been required to practice the invention at the time of filing.

f) Predictability in the Art: It has been well known that minor structural differences even among structurally related proteins can result in substantially different binding activities for the same antibody. For example, Lederman et al (Molecular Immunology 28:1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Li et al (Proc. Natl. Acad. Sci. USA 77:3211-3214, 1980) disclose that dissociation of immunoreactivity from other activities when constructing analogs (see entire document).

Adequate written description for an antibody appears to hinge upon whether the specification provides adequate written description for the antigen. While a specification may enable making a genus of antibodies, this does not necessarily place applicant in possession of the resultant antibodies (See *In re Kenneth Alonso* October (Fed. Cir. 2008) sustaining a lack of adequate written description rejection where "the specification teaches nothing about the structure, epitope characterization, binding affinity, specificity, or pharmacological properties common to the large family of antibodies" where the specification does not characterize the antigens to which the monoclonal antibodies must bind).

Applicants have not characterized the breadth of tumor marker protein antigens to which the breadth of anti-tumor autoantibodies should bind, and therefore, the ordinary artisan could reasonably conclude that Applicants were not in possession of the claimed genus of tumor marker protein antigens much less the autoantibodies that are

reactive against those proteins.

Applicants are requested to please carefully take note of the Alonso decision with respect to their own claims."

The rejection was maintained in the Office Action of 8/30/10 as follows:

"Applicants allegations on pp. 11-12 of the Response of 3/8/10 have been considered and are not found persuasive. Applicants allege the present application contains working examples, clearly describes the source of antigen as being from a bodily fluid from a body cavity or space in which a tumor is or was present in one or more cancer patients, lists five exemplary bodily fluid useful as sources of the tumor marker protein (ascites, pleural effusion, seroma, hydrocoele and wound drainage fluid), and lists numerous tumor marker proteins with reference to scientific publications that describe these tumor marker proteins in detail.

Response to Arguments

In order to meet the structure/function requirement and to show possession and contemplation under the written description guidelines, Applicants must show the method can detect a reasonable number of species for anti-tumor marker autoantibodies against the universe of over-expressed tumor-marker proteins much less any altered forms of wild-type proteins. Applicants have not addressed the frequency at which autoantibodies are generated against over-expressed tumor markers much for modified wild-type proteins in order for the ordinary artisan to conclude that Applicants were in possession of the full scope of the method.

In addition, see *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.* (Fed. Cir. 2010) (en banc) stating in part: "a few broad principles hold across all cases"; "We have made clear that the written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement. *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366-67 (Fed. Cir. 2006). Conversely, we have repeatedly stated that actual "possession" or reduction to practice outside of the specification is not enough. Rather, as stated above, it is the specification itself that must demonstrate possession. And while the description requirement does not demand any particular form of disclosure, *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008), or that the specification recite the claimed invention *in haec verba*, a description that merely renders the invention obvious does not satisfy the requirement, *Lockwood v. Am. Airlines*, 107 F.3d 1565, 1571-72 (Fed. Cir. 1997)."

"For example, a generic claim may define the boundaries of a vast genus of chemical compounds, and yet the question may still remain whether the specification, including original claim language, demonstrates that the applicant has invented species sufficient to support a claim to a genus. The problem is especially acute with genus claims that use functional language to define the boundaries of a claimed genus. In such a case, the functional claim may simply claim a desired result, and may do so without describing species that achieve that result. But the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus."

Applicants allegations on pp. 11-12 of the Response of 8/30/10 have been considered and are not found persuasive. Applicants proffer the same arguments from the Response of 3/8/10.

Response to Arguments

The examiner proffer's the same arguments from the Office Action of 8/30/10 for purposes of brevity. Finally, as discussed in the interview of 8/25/10 and excerpted from the Advisory Action of 9/27/10 "the tumor marker proteins must meet the following structure/function criteria under the instant claims: i) found in bodily fluid/space/cavity around a tumor, ii) over-expressed by the tumor, iii) altered forms of a wild type tumor protein are found/isolated, and iv) the tumor antigen (wild-type or mutant) must be auto-reactive/ antigenic in order to generate auto-antibodies. The nature and kind of tumor antigens encompassed by the claims would require undue experimentation to identify a tumor protein meeting all of the structure/function requirements."

The rejection is maintained.

Conclusion

10. No claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on 571-272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/
Primary Examiner, Art Unit 1643